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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,472	04/16/2004	Michelle L. Monje	STAN-303 (S03-066)	1490

77974 7590 02/17/2011

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
02/17/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,472	MONJE ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,14,21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,14, 21,23-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 June 2010 has been entered.

Status of Claims

2. The amendments filed on 6 May 2010 and 22 June 2010 have been entered into the record and have been fully considered.

3. Claim 1 is amended. Claim 22 is canceled. New claims 23 and 24 have been added.

4. Claims 1, 3-5, 14, 21 and 23-24, drawn to a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation, are being considered for examination in the instant application.

5. Claims 7 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 15 June 2007.

Response to Amendment

Withdrawn objections and/or rejections

6. Upon consideration of amendment of independent claim 1 to introduce an additional step of measuring cognitive function after administration of NSAID, all pending obviousness rejections have been withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 3-5, 14, 21, 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (J Med Primatol 30: 81-87, 2001), and Plevova, (Radiol Oncol 36: 33-40, 2002), in view of Rogers et al. (Neurology 43: 1609-1611, 1993 – listed in IDS dated 11/9/04).

9. The claims recite a method of reducing loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation in an individual, comprising identifying an individual at risk for having loss of neurogenesis from chronic neuroinflammation due to cranial irradiation; contacting the individual with non-steroidal anti-inflammatory drug (NSAID), indomethacin (claims 1, 21, 23, 24) such that it crosses the BBB; measuring cognitive function following cranial irradiation wherein a decline in cognitive function is linked to impaired neurogenesis with the central nervous system (claim 14). Claim 23 further recites that the NSAID is administered on a daily or a semi-daily basis for one or more months. The claims further recite that the inflammation and microbial activation results from cranial ionizing radiation, and the anti-inflammatory agent is contacted prior or subsequent to the irradiation (claims 3-5).

10. Price et al. teach that neuroinflammation is observed after irradiation of the brain (i.e. CNS) in primates resulting in the activation of microglia/ macrophages (abstract). Price et al. also demonstrate acute and long-term histopathological changes of different regions of the irradiated brain (white matter and meninges) (page 83, Results, para 1; Table 2), resulting in gliosis and demyelination, which are underlying causes for CNS radiation induced cognitive

impairment (page 86, Discussion, para 1), thereby indicating a loss of neurogenesis. Therefore, Price et al. teachings have identified an individual with chronic neuroinflammation due to cranial irradiation, who is inherently at risk for suffering from loss of neurogenesis.

11. Price et al. do not teach administering an NSAID and do not teach measuring cognitive decline.

12. Plevova teaches that ionizing radiation results in an inflammatory reaction and cellular damage, an effect that is inhibited by corticosteroids and NSAID (abstract).

13. Plevova does not teach measuring cognitive decline.

14. Rogers et al. teach the use of indomethacin (a NSAID) for the treatment of Alzheimer's disease (AD) in a clinical trial. The reference teaches administering indomethacin or placebo to AD patients daily for 6 months, and conducting tests for measuring cognitive function. The results elicit an improved cognitive function in the indomethacin group versus the placebo controls (abstract; Table). Because the administered doses of indomethacin improved progressive cognitive decline resulting from neuroinflammatory activity, the doses are considered to be effective for the same. It is well established that indomethacin crosses the blood-brain barrier (BBB).

15. Rogers et al do not teach administering the drug to patients with cognitive decline due to cranial irradiation.

16. Rogers et al., Price et al or Plevova do not actually teach contacting the individual with NSAID before or after irradiation.

17. However, since the claims do not specify the criticality in the timing (i.e. before or after irradiation) of contacting the individual with NSAID, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art.

As stated in MPEP 2144.05:

The differences in time will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such timing is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages". *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

18. It would have been obvious to one of ordinary skill in the art to administer an NSAID to patients who have had cranial irradiation. The person of ordinary skill would be motivated in view of the combined teachings of Price et al and Plevova who indicate that this form of irradiation induces inflammation, and that such inflammation can be attenuated with NSAIDs. The step of measuring cognitive decline following NSAID administration in patients with neurological disorders mediated inflammation as provided by Rogers et al. would have been obvious as it would be an easy, non-invasive method to monitor the efficacy of the NSAID therapy. Additionally, it would have been obvious to determine the optimal timing of contacting an individual with NSAID, i.e. before or after

irradiation, in view of the teachings of Price et al, Plevova and Rogers et al. The person of ordinary skill in the art would have been motivated to perform the steps of administering NSAID and measuring cognitive decline in individuals subjected to cranial irradiation, because both cranial radiation and AD are known to result in neuroinflammation that can be prolonged or become chronic as taught by Price et al above. The person of ordinary skill in the art would have expected success because the inflammatory effects of irradiation as well as the anti-inflammatory effects of indomethacin were well known at the time the invention was made.

19. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's remarks

20. Highlighting the amendments, Applicant asserts the salient features of the invention and alleges that the Patent Office "must show that the ordinarily skilled artisan has performed the steps of the invention" to render the claims as anticipatory or obvious. Applicant argues that the skilled artisan would require the insight and knowledge that cranial irradiation induces chronic neuroinflammation resulting in loss of neurogenesis, and that NSAIDs can interfere with the loss of neurogenesis. Applicant indicates that the loss of neurogenesis is measurable as progressive decline in cognitive function. Applicant alleges that a person of ordinary skill "would not be able to predict form the cited combinations of art that

a progressive decline in cognitive function due to cranial irradiation-induced chronic neuroinflammation could be reduced by administering an NSAID".

21. On page 7 of the "Remarks" Applicant explains that certain brain regions (e.g. CA1 zone of hippocampus, cortex/entorhinal cortex, lateral striatum) have mature neurons and do not demonstrate neurogenesis, while the dentate gyrus and subventricular zone of the hippocampus elicit neurogenesis. Applicant therefore, argues that since the skilled artisan would know as to which brain regions should be looked into for neurogenesis, reciting such limitations in the claims is not necessary. Arguing that the current amendment of measuring cognitive function would indicate progressive cognitive decline as a "surrogate marker for impaired neurogenesis", Applicant emphasizes that "no step of measuring loss of neurogenesis per se is necessary".

22. Applicant's arguments are fully considered, however, are not found to be persuasive. Applicant has correctly specified the active steps, i.e. identifying an individual subjected to cranial irradiation, administering NSAID that crosses the BBB effective to reduce neuroinflammatory activity, and measuring cognitive function following irradiation to determine a progressive decline in said function. Although none of the references are explicitly teaching "loss of neurogenesis" in subjects with cranial irradiation, and further a method for reducing the same, it is noted that the active steps of the claims do not require looking into the loss of neurogenesis. No direct nexus between neuroinflammation and loss of neurogenesis is derived from the instant claims as recited. The limitation

"wherein said loss of neurogenesis resulting from chronic neuroinflammation due to said cranial irradiation in an individual is reduced" in claim 1, is recited as an intended outcome of the process, that essentially goes back to the preamble of the claim. It is reminded that "where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation" *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997). As rightly pointed by Applicant, the claims require 3 main steps **- identifying** a person subjected to cranial irradiation (who would inherently be at risk of neuroinflammation and loss of neurogenesis); **contacting** the individual with NSAID and; **measuring** cognitive function. Claims 1 and 23 recite that the "progressive decline in cognitive function is linked to impaired neurogenesis", in other words, a decline in cognitive function would correspond to loss of neurogenesis. The person of ordinary skill would find it obvious to administer NSAID to an individual subjected to cranial irradiation, a state known to elicit neuroinflammation, whereby the inflammation is reduced, thus leading to a decrease in loss of neurogenesis.

23. Furthermore, Applicant's allegation that in order to consider the invention as obvious, the skilled artisan should have insight and knowledge that cranial irradiation induces chronic neuroinflammation resulting in loss of neurogenesis, and that NSAIDs can interfere with the loss of neurogenesis, is not persuasive. Applicant is arguing mechanistic issues, i.e. cranial irradiation results in loss of

neurogenesis. Adequate reasoning has been provided to show that the references teach all method steps as recited in the claims including the step of measuring cognitive decline representing loss of neurogenesis. Applicant's arguments on the relationship between cranial irradiation and loss of neurogenesis is therefore, moot as this embodiment is not required by the instant claim limitations. Moreover, the amended claims recite that the loss of neurogenesis can be determined by measuring cognitive function in said population. Applicant is claiming a surprising discovery involving a novel mechanism comprising the loss of neurogenesis resulting from irradiation, which can be determined by measuring cognitive function. However, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

24. Applicant's remarks that the claims would not need an additional step of measuring loss of neurogenesis per se, because the skilled artisan would know which regions of the brain to look for neurogenesis, and because the amended claims require measuring cognitive function as a surrogate marker for the same is acknowledged. Applicant's comments are considered, however, are moot in context with the current amendments. It is repeated that all three steps involving identifying, administering and measuring are rendered obvious by the combined teachings of Rogers et al., Price et al and Plevova for reasons explained above,

therefore, the aspect of loss of neurogenesis would naturally flow from accomplishing the method steps.

Conclusion

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

27. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
9 February 2011

/Daniel E Kolker/

Primary Examiner, Art Unit 1649

February 14, 2011